TRANSLATION OF

DE 3,445,011 A1

Applicant: CIBA-GEIGY AG

Publication Date: June 13, 1985

GERMAN PATENT OFFICE

DE 3445011 A1

Int. Cl.: **C 07 C 101/447**

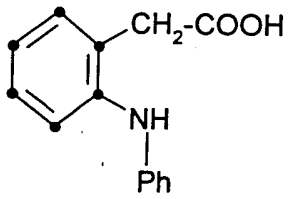
File reference: P 34 45 011.4
Application date: 10.12.84
Publication date: 13.06.85

Priority: 13.12.83 CH 6639/83-8

Applicant: CIBA-GEIGY AG, Basle, CH

Title: New aniline derivative, process for its production and its use.

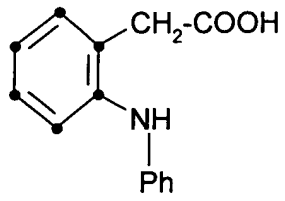
New aniline derivative of formula



wherein Ph is 2,6-difluorophenyl, and the salts thereof, exhibit anti-inflammatory and analgesic properties and may be used as active ingredients for medicaments. The compounds of formula (I) and salts thereof are produced by processes known *per se*.

Patent Claims

1. New aniline derivative of formula



(I)

wherein Ph is 2-chloro-6-fluorophenyl, and the salts thereof.

2. Compound according to claim 1 having anti-inflammatory and/or analgesic activity.

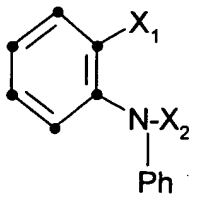
3. The new compounds named in examples 1-2.

4. Compound according to claim 1 or 2 in a process for the therapeutic treatment of the human or animal body.

5. Pharmaceutical preparations containing a compound according to one of claims 1-4 together with customary pharmaceutical excipients and substrates.

6. Process for the production of the compound according to claim 1 or of a salt thereof, characterised in that

a) compounds of formula



(II)

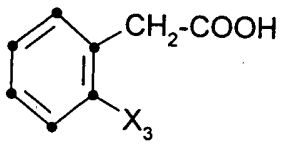
or a salt thereof,

wherein X_1 signifies a radical that can be converted into the group of formula $-CH_2-COOH$ and X_2 is hydrogen, or wherein X_1 and X_2 together signify an oxo-ethylene group which is linked by the carbonyl-carbon atom to the anilino-nitrogen atom, or represent a group of formula $-CH=C(R_1)-P(=O)(OR_2)-$ which is linked by the phosphorus atom to the anilino-nitrogen atom,

whereby R_1 is a disubstituted amino group and R_2 is alkyl, or wherein X_1 signifies the group of formula $-CH_2-COOH$ and X_2 is an appropriate amino protecting group that can be replaced by hydrogen,

are converted into the compound of formula (I) or a salt thereof, or

b) a compound of formula



(IIIa)

or a salt thereof, is reacted with a compound of formula

$$Ph\text{-}X_4 \qquad \text{(IIIb)}$$

or with a salt thereof, wherein one of radicals X_3 and X_4 signifies halogen and the other signifies amino, and/or, if desired, a salt obtainable in accordance with the process is converted into the free compound or into another salt, or the free compound obtainable in accordance with the process is converted into a salt.

7. Process according to claim 6, characterised in that a compound of formula II is converted into the compound of formula (I) by hydrolysis, acidolysis, reduction or oxidation.

8. Process according to claims 1 and 2, characterised in that the process starts with a compound obtainable as an intermediate at any stage of the process and the missing steps are then carried out, or a starting material is used in the form of a salt and/or racemate or antipodes or, in particular, is formed under the reaction conditions.

9. Process for the production of pharmaceutical preparations, characterised in that a compound according to one of claims 1-4 is mixed with conventional excipients and substrates.

10. Use of compounds according to one of claims 1, 2 or 4 in a process for the treatment of inflammatory and/or rheumatic illnesses and/or painful conditions.

11. The process of examples 1-2 and the new compounds obtainable thereby.

12. The new compounds obtainable by the process according to one of claims 6-8.

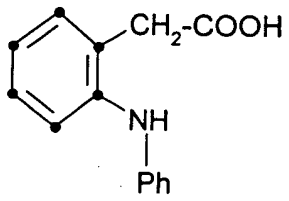
13. The starting materials and intermediates used in the processes according to one of claims 6-8, as well as processes for the preparation thereof.

3445011

CIBA-GEIGY AG
Basle (Switzerland)

New aniline derivative, process for the production thereof and the use thereof

The invention relates to a new aniline derivative of formula



(I)

wherein Ph is 2-chloro-6-fluorophenyl, and the salts thereof, process for the production thereof, the use thereof, e.g. as active ingredients for medicaments in the treatment of illnesses, as light protecting agents and/or for the production of pharmaceutical preparations or light protecting agents, as well as pharmaceutical preparations and/or light protecting agents which contain this compound or the salts thereof.

The salts of the compound according to the invention may be in particular salts with bases; corresponding pharmaceutically acceptable salts are preferred.

Suitable salts with bases are e.g. corresponding metal salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, aluminium or transition metal salts such as zinc or copper salts, or corresponding salts with ammonia or organic amines. The organic amines may be e.g. the following: alkylamines such as mono-, di- or tri-lower alkylamines, alkylene diamines such as lower alkylene diamines, phenyl-substituted alkyl amines such as mono- or di-phenyl-lower-alkylamines, hydroxyalkylamines such as mono-, di- or trihydroxy-lower-alkylamines, an oligohydroxy-lower-alkylamine or hydroxy-lower-alkyl-di-lower-alkylamines, amino sugars, e.g. those whose amino group may be optionally substituted by at least one lower alkyl radical, cycloalkylamines such as mono- or dicyclo-lower-alkylamines, basic amino acids, cyclic amines such as lower alkylene- or lower alkenylene-amines with 2 to 6 C-atoms, whereby the carbon chain may also be interrupted by aza, N-lower-alkyl-aza, oxa and/or thia. Mono-, di- or tri-lower-alkylamines are e.g. ethyl- or tert.-butylamine, diethyl- or diisopropylamine, trimethyl- or triethylamine, and lower-alkylenediamine is e.g. ethylenediamine. Mono- or di-phenyl-lower-alkylamines may be e.g. benzyl- or 1- or 2-

phenylethyl-amine or dibenzylamine. Mono-, di- or trihydroxy-lower-alkylamines are e.g. mono-, di-, tri-ethanolamine or diisopropanolamine, an oligohydroxy-lower-alkylamine, e.g. tris-(hydroxymethyl)-methylamine and hydroxy-lower-alkyl-di-lower-alkylamines e.g. N,N-dimethyl- or N,N-diethylaminoethanol. Amino sugars are derived e.g. from monosaccharides, in which an alcoholic hydroxyl group is replaced by an amino group, such as D-glucosamine, D-galactosamine or D-mannosamine. N-methyl-D-glucosamine may be mentioned as an example of a N-lower-alkylated amino sugar. Mono- or dicyclo-lower-alkylamine is e.g. cyclohexyl- or dicyclohexylamine. Basic amino acids are e.g. arginine, histidine, lysine or ornithine. Lower alkyleneamines or lower alkenyleneamines with 2 to 6 C-atoms are e.g. azirine, pyrrolidine, piperidine or pyrroline, and the lower alkyleneamines or lower alkenyleneamines whose carbon chain is interrupted by aza, N-lower-alkylaza, oxa and/or thia may be e.g. imidazoline, 3-methyl-imidazoline, piperazine, 4-methyl- or 4-ethyl-piperazine, morpholine or thiomorpholine.

Furthermore, for salt formation, urotropine may be used for example, as well as bases having local anaesthetic action, such as procaine.

In US patent specification no. 3.558.690, for example, a compound which is analogous to the compound according to the invention is described. This is 2-(2,6-dichloroanilino)-phenylacetic acid (diclofenac). The sodium salt of diclofenac (diclofenac sodium) is used e.g. as an anti-rheumatic having marked anti-inflammatory and analgesic activity.

The compound of formula (I) or a salt thereof has marked anti-inflammatory activity, for example the significant inhibition of the carrageenin-induced paw oedema of the rat, analogously to the method described by Pasquale et al., Agents and Actions 5, 256 ff. (1975).

Furthermore, the compound of formula (I) has an antinociceptive (analgesic) active component which can be detected e.g. by a reduction in the phenyl-p-benzoquinone-induced writhing syndrome on the mouse, according to the method of L.C. Hendershot and J. Forsaith, J. Pharmacol. exp. Therap. 125, 237 ff. (1959).

In the models mentioned, the sodium salt of the compound of formula (I) has e.g. the same degree of activity as diclofenac sodium.

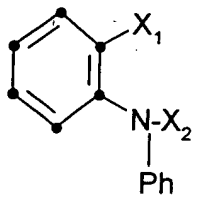
In a direct comparison of the sodium salt of the compound of formula (I) with diclofenac sodium during investigations of gastro-intestinal tolerance, which were carried out analogously to Lee et

al., Arch. Internat. Pharmacodyn. 192, 370 (1971), for the sodium salt of the compound of formula I a more favourable ulcus index was determined than for diclofenac sodium. This means that the corresponding compound according to the invention, can be better tolerated than diclofenac sodium, for example when given orally to the rat.

Surprisingly, the compound of formula (I) has proved to be considerably more water-soluble than diclofenac. For example, at 37°C, a water-solubility of 6.6 g/100 ml was determined for the sodium salt of the compound of formula (I) and for diclofenac sodium it was 2.25 g/100 ml. This has the advantage that only relatively small amounts of liquid are required especially for intra-muscular application by means of injection solutions. In this way, unpleasant local irritation is substantially eliminated.

The compounds of the present invention and their salts may be produced by processes known *per se*, e.g. whereby

a) compounds of formula



(II)

or a salt thereof,

wherein X_1 signifies a radical that can be converted into the group of formula $-CH_2-COOH$ and X_2 is hydrogen, or wherein X_1 and X_2 together signify an oxo-ethylene group which is linked by the carbonyl-carbon atom to the anilino-nitrogen atom, or represent a group of formula $-CH=C(R_1)-P(=O)(OR_2)-$ which is linked by the phosphorus atom to the anilino-nitrogen atom, whereby R_1 is a disubstituted amino group and R_2 is alkyl, or wherein X_1 signifies the group of formula $-CH_2-COOH$ and X_2 is an appropriate amino protecting group that can be replaced by hydrogen,

are converted into the compound of formula (I) or a salt thereof, or

b) a compound of formula

Esterified carboxyl is for example carboxyl esterified with an aliphatic alcohol. An aliphatic alcohol may be for example a lower alkanol which is optionally substituted e.g. by aryl, such as phenyl. Carboxyl esterified in this way is for example lower alkoxycarbonyl or phenyl-lower-alkoxycarbonyl.

Amidated carboxyl has as the amino group a free, mono- or di-substituted amino group; the substituents may be for example aliphatic radicals, such as optionally substituted lower alkyl. A corresponding amidated carboxyl is for example carbamoyl, N-mono- or N,N-di-lower-alkyl-carbamoyl, such as N,N-dimethylcarbamoyl.

Anhydridised carboxyl is for example carboxyl anhydridised with a mineral acid such as hydrohalic acid, or with a carboxylic acid such as an optionally substituted lower alkane-carboxylic acid or benzoic acid or a carbonic acid lower alkyl semi-ester. Examples that may be mentioned are halocarbonyl such as chlorocarbonyl, lower alkanoyloxycarbonyl such as acetyloxycarbonyl, or lower alkoxycarbonyloxycarbonyl such as ethoxycarbonyloxycarbonyl.

Optionally substituted amidino is for example amidino substituted by an aliphatic, e.g. lower alkyl, radical, such as amidino or lower alkylamidino, e.g. ethylamidino.

Optionally esterified thiocarboxyl or dithiocarboxyl contains for example the alcohol or hydroxyl components named for example in connection with esterified carboxyl. Examples taken from these are lower alkylthiocarbonyl such as ethylthiocarbonyl, lower alkoxythiocarbonyl such as ethoxythiocarbonyl, lower alkylthio-thiocarbonyl such as ethylthio-thiocarbonyl, the respective thiocarboxyl and dithiocarboxyl.

Optionally substituted thiocarbamoyl may have e.g. the substituents named for amidated carboxyl. Examples that may be mentioned are N-mono- or N,N-di-lower-alkyl-thiocarbamoyl such as methyl- or diethyl-thiocarbamoyl, as well as thiocarbamoyl or morpholino-thiocarbonyl.

By alkoxy- or halo-formimidoyl is understood for example lower alkoxy-, such as ethoxy-, or chloro-formimidoyl, while corresponding 2-oxazolidinyl and 2-oxazinyl groups are e.g. 1,3-oxazin-2-yl, 4,4-, 5,5-dimethyl- or 4,6,6-trimethyl-1,3-oxazin-2-yl.

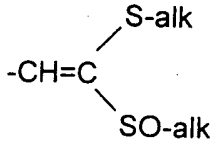
Trihalo- or trialkoxy-methyl is for example trichloromethyl or tri-lower-alkoxy- such as trimethoxy-methyl.

An amino protecting group X_2 that can be converted by hydrolysis into hydrogen is for example an appropriate acyl radical. A preferred acyl radical is one which is derived from an organic carboxylic acid, such as a lower alkanecarboxylic acid that is optionally substituted e.g. by halogen or aryl, or a benzoic acid that is optionally substituted e.g. by halogen, lower alkoxy or nitro. Such acyl radicals are e.g. lower alkanoyl such as formyl or acetyl, halo-lower-alkanoyl such as trifluoroacetyl, or benzoyl that is optionally substituted e.g. by halogen, lower alkoxy or nitro, such as benzoyl, 4-chlorobenzoyl, 4-methoxy- or 4-nitrobenzoyl, and furthermore lower alkoxycarbonyl, e.g. ethoxycarbonyl.

Hydrolysis is effected in a manner known *per se* with the assistance of water, the process being advantageously carried out in the presence of an acid or base that supports hydrolysis, optionally in the presence of an inert solvent or diluent and/or whilst cooling or heating.

Suitable acids are for example inorganic or organic protonic acids, such as mineral acids, e.g. sulphuric acid, a phosphoric acid or a hydrohalic acid, sulphonic acid, e.g. lower alkane- or optionally substituted benzenesulphonic acids, for example methane- or p-toluenesulphonic acid, or carboxylic acids, e.g. optionally substituted lower alkane-carboxylic acids, for example acetic acid or trifluoroacetic acid. The bases which may be used are for example alkali metal hydroxides or alkaline earth metal hydroxides or carbonates, such as sodium, potassium or calcium hydroxide, sodium or potassium carbonate.

In this way, hydrolysis of compounds of formula (II), wherein X_1 is the group of formula $-CH_2-Y_1$, Y_1 signifying for example esterified, amidated, anhydridised carboxyl, cyano, optionally substituted amidino, optionally esterified thiocarboxyl or dithiocarboxyl, optionally substituted thiocarbamoyl, substituted formimidoyl, and X_2 is hydrogen, may be carried out both in the presence of an acid or in particular in the presence of a base. The hydrolysis of compounds of formula (II), wherein X_1 is e.g. the group of formula $-CH_2-Y_1$ and Y_1 is e.g. trihalo- or trialkoxy-methyl, or wherein X_1 represents e.g. a group of formula $-CH=C(Hal)_2$, or



and X_2 is hydrogen, may be preferably carried out in the presence of an acid. The hydrolysis of compounds of formula (II), wherein X_1 and X_2 together signify an oxo-ethylene group which is linked by the carbonyl-carbon atom to the anilino-nitrogen atom, or represent a group of formula $-CH=C(R_1)-P(=O)(OR_2)-$ which is linked by the phosphorus atom to the anilino-nitrogen atom, or wherein X_1 signifies the group of formula $-CH_2-COOH$ and X_2 is an acyl radical, may be preferably effected in the presence of a base.

A radical X_1 that can be converted by acidolysis into the group of formula $-CH_2-COOH$ may be for example a group of formula $-CH_2-Y_1$, wherein Y_1 is e.g. carboxyl, which is esterified with a tertiary or secondary alcohol, such as a corresponding lower alkanol which is optionally substituted by aryl, in particular tert.-butanol, 2-biphenyl-propan-2-ol or diphenyl-methanol.

An amino protecting group X_2 that can be replaced by hydrogen by means of acidolysis is for example an acyl group, especially one that is derived from a carbonic acid semi-ester such as a lower alkyl carbonic acid semi-ester which is optionally substituted, for example by halogen or aryl, or a phenylthio group which is optionally substituted, in particular by nitro. Such groups are understood to be e.g. in particular branched lower alkoxycarbonyl that is optionally substituted, e.g. by aryl, such as tert.-butyloxy-, 2-biphenyl-2-propyloxy- or diphenylmethoxycarbonyl, 1-phenyl-lower-alkoxycarbonyl that is optionally substituted, e.g. by halogen, lower alkoxy or nitro, such as benzyloxy-, diphenylmethoxy- or 4-nitro-benzyloxy-carbonyl, as well as 2-nitro- or 2,4-dinitrophenylthio.

Preferred amino protecting groups in this instance are e.g. tert.-butyloxy- or benzyloxycarbonyl.

During acidolytic cleavage, normally strong protonic acids are used, such as mineral acids, for example the hydrohalic acids hydrochloric, hydrobromic or hydriodic acid, perchloric acid, optionally suitably substituted lower alkanecarboxylic acids, such as formic acid, glacial acetic acid or trifluoroacetic acid, sulphonic acids such as optionally substituted phenylsulphonic acids, e.g. p-bromophenyl- or p-toluenesulphonic acid, or mixtures thereof, such as mixtures of hydrobromic acid and glacial acetic acid. Acidolysis may be optionally carried out in an inert solvent such as an ether, e.g. anisole, and if necessary with heating; the corresponding acid may also be advantageously used as solvent.

A radical X_1 that can be converted by reduction into the group of formula $-CH_2-COOH$ may be for example a group of formula $-CH_2-Y_1$, wherein Y_1 is for example an acyl group which is derived

from an aryl-substituted lower alkyl carbonic acid semi-ester, such as 1-aryl-lower-alkoxy-carbonyl, or an acyl group that is derived e.g. from a carbonic acid semi-ester which is optionally substituted, e.g. by halogen, such as lower alkoxycarbonyl substituted once or more by halogen, or it is a 1-(arylcarbonyl)-lower-alkoxycarbonyl group. 1-aryl-lower-alkoxycarbonyl signifies e.g. 1-phenyl-lower-alkoxycarbonyl which is optionally substituted, e.g. by nitro or lower alkoxy, such as benzyloxy-, 4-nitro- or 4-methoxybenzyloxycarbonyl, and lower alkoxycarbonyl which is substituted once or more by halogen, e.g. 2-iodethoxy- or trichlorethoxycarbonyl. 1-(aryl-carbonyl)-lower-alkoxycarbonyl is e.g. phenacyloxycarbonyl which is optionally substituted in the phenyl moiety, e.g. by halogen, such as 4-chlorophenacyloxycarbonyl.

An amino protecting group X_2 which can be replaced by hydrogen by means of reduction is for example an acyl group which is derived from a carbonic acid semi-ester, especially an aryl-substituted lower alkylcarbonic acid ester, or which is formed from an organic sulphonic acid, such as arylsulphonic acid, as well as 1-aryl-lower-alkyl or 2-lower-alkenyl. In this instance, acyl groups which are derived from a lower alkylcarbonic acid ester which is substituted by aryl or halogen are for example 1-phenyl-lower-alkoxycarbonyl optionally substituted e.g. by halogen, lower alkoxy or nitro, such as benzyloxy-, diphenylmethoxy- or 4-nitrobenzyloxy-carbonyl, or halogen-lower-alkoxycarbonyl such as trichlorethoxy- or iodethoxycarbonyl, and acyl groups which are formed e.g. from an arylsulphonic acid, such as phenylsulphonyl which is optionally substituted, e.g. by halogen or lower alkyl, such as p-bromophenylsulphonyl or p-toluenesulphonyl. 1-aryl-lower-alkyl is for example 1-phenyl-lower-alkyl which is optionally substituted, e.g. by lower alkoxy, such as benzyl, and 2-lower-alkenyl is in particular allyl.

Preferred groups X_1 which can be converted into the group of formula $-CH_2-COOH$ by reduction are e.g. those groups of formula $-CH_2-Y_1$ wherein Y_1 signifies benzyloxycarbonyl which is optionally substituted by lower alkyl or by nitro, as well as trichloroethoxy- or 2-iodoethoxy-carbonyl. Preferred amino protecting groups X_2 that can be cleaved by reduction are for example benzyl or allyl, and also p-toluenesulphonyl or 2-nitrophenylthio.

Depending on the reducible groups X_1 or X_2 that are chosen, reduction of corresponding compounds of formula (II) may take place for example by hydrogenolysis, by reduction with metallic systems, by appropriate noble metal catalysts, and by dithionites.

Radicals X_1 which can be converted hydrogenolytically into the group of formula $-CH_2-COOH$ are for example groups of formula $-CH_2-Y_1$, wherein Y_1 is an acyl group which is derived e.g.

from an aryl-substituted lower-alkylcarbonic acid semi-ester, for example 1-aryl-lower-alkoxy-carbonyl, such as 1-phenyl-lower-alkoxycarbonyl which is optionally substituted, e.g. by nitro or by lower alkoxy, especially benzyloxycarbonyl. Hydrogenolytically cleavable amino protecting groups X_2 which may be named are for example acyl groups which are derived from an aryl-substituted lower alkylcarbonic acid semi-ester, such as optionally substituted 1-phenyl-lower-alkoxycarbonyl, especially benzyloxycarbonyl, or 1-aryl-lower-alkyl, such as optionally substituted 1-phenyl-lower-alkyl, especially benzyl.

Hydrogenolysis is carried out for example with hydrogen in the presence of a catalyst. The catalyst may be for example an element of the 8th secondary group of the Periodic Table or a derivative thereof, e.g. oxide, such as platinum, palladium, nickel, e.g. in the form of Raney nickel, or platinum oxide. Such catalysts may be applied e.g. to suitable substrates, such as carbon, barium carbonate or calcium carbonate, and also silicaceous earth. Hydrogenolysis may be optionally carried out with heating and/or under pressure, as well as under an inert gas such as nitrogen. It is carried out in particular at temperatures between ca. -80° and 200°C, especially between room temperature and ca. 100°C, and at pressures of between ca. 1 and 100 atm. The reaction is conveniently carried out in the presence of a solvent such as water, an alcohol such as lower alkanol, or an ether such as dioxane or tetrahydrofuran.

Radicals X_1 which can be converted by appropriate metallic systems into the group of formula $-CH_2-COOH$ are for example groups of formula $-CH_2-Y_1$, wherein Y_1 are e.g. acyl groups which are derived from a carbonic acid semi-ester substituted by aryl or halogen, or wherein Y_1 signifies e.g. arylcarbonyl lower alkoxycarbonyl. Corresponding radicals X_2 are for example acyl groups which are derived from an aryl-substituted carbonic acid semi-ester or which are formed from an arylsulphonic acid.

Metallic systems that are suitable for reduction are made up e.g. of a metal component and a hydrogen-yielding component. The metal component consists e.g. of a non-noble metal, such as an alkali metal, iron, zinc or tin, chromium(II) salts, e.g. chromium(II) chloride, or an alloy, such as aluminium-nickel alloy, sodium- or aluminium-amalgam. The hydrogen-yielding component is composed e.g. of an inorganic or organic protonic acid, such as mineral acid, or optionally hydroxy-substituted carboxylic acid, e.g. acetic acid, glycolic acid, malic acid, mandelic acid or tartaric acid, or of an alkali metal hydroxide solution, e.g. sodium or potassium hydroxide, an alcohol such as lower alkanol, e.g. methanol, ethanol or tert.-butanol to which water is optionally added, or water optionally mixed with a lower alkanol, or ammonia. Examples of such systems

are zinc/hydrochloric acid, glacial acetic acid, glycolic acid, mandelic acid, malic acid or tartaric acid, iron/hydrochloric acid, tin/hydrochloric acid or glacial acetic acid, sodium/ammonia, zinc/sodium hydroxide. Systems may also be used, which consist of alkali metal with lower alkanols, e.g. sodium with ethanol or tert.-butanol, aluminium-nickel alloys in aqueous-alkaline solution, to which a lower alkanol may be optionally added, as well as sodium- or aluminium-amalgam in aqueous-alcoholic or aqueous solution. Preferred systems which may be named are zinc/hydrochloric acid or glacial acetic acid or sodium/ammonia.

The metallic reduction systems may also include for example those which consist of a non-noble metal, such as zinc, and a thiole such as thiophenol.

Further reduction agents which are especially suitable for the cleavage of 2-lower-alkenyl X_2 are for example noble metal catalysts, such as rhodium(III) halides, e.g. rhodium(III) chloride.

For the conversion by reduction of groups of formula X_1 wherein X_1 is the group of formula $-CH_2-Y_1$ and Y_1 is e.g. 1-(arylcarbonyl)-lower-alkoxycarbonyl, dithionites may similarly be used, such as alkali metal dithionites, e.g. sodium or potassium dithionite. The process takes place in particular under basic conditions.

Compounds that may similarly be converted by reduction into the compound of formula (I) or a salt thereof are for example those of formula (II), wherein X_1 is a group of formula $-CH(Y_2)-COOH$, in which Y_2 is a radical that can be replaced by hydrogen, or wherein X_1 is a group of formula -A-COOH, in which A is a group that can be converted into methylene, and X_2 respectively signifies hydrogen.

A radical Y_2 that can be replaced by hydrogen is for example hydroxyl, lower alkylthio, especially methylthio, di-lower-alkylamino, especially dimethylamino, diphenylsulphamoyl which is optionally substituted in the phenyl moiety, especially di-(p-toluene)-sulphamoyl or di-(p-bromo-phenyl)-sulphamoyl, or carboxyl. A grouping -A- that can be converted into methylene signifies for example carbonyl or optionally substituted hydrazonomethylene, such as lower alkyl-hydrazonomethylene, phenylhydrazonomethylene which is optionally substituted in the phenyl moiety or sulphonyl-hydrazonomethylene, especially p-toluenesulphonyl-hydrazonomethylene.

The reduction agent employed may be for example elementary hydrogen which is activated by a hydrogenation catalyst, and also an optionally complex hydride or red phosphorus in the

presence of hydrogen iodide or iodine. Appropriate hydrogenation catalysts are for example elements of the 8th secondary group of the Periodic Table or derivatives thereof, e.g. a corresponding oxide. Examples of such hydrogenation catalysts are platinum, platinum oxide, palladium or Raney nickel. Such catalysts may be applied to a substrate such as activated carbon, an alkaline earth metal carbonate or sulphate, as well as a silica gel. The optionally complex hydrides may be for example hydrides of elements of the first to third main group or complex hydrides formed therefrom, such as diboran, aluminium hydride, lithium or sodium borohydride, lithium or sodium aluminium hydride, and also organometallic hydrides, such as lithium triethylborohydride.

In a preferred embodiment of the process, hydroxyl, lower alkylthio, especially methylthio, as well as di-lower-alkylamino, especially dimethylamino, are reduced with catalytically activated elementary hydrogen, whereby the hydrogenation catalyst used is e.g. palladium/carbon or Raney nickel. Furthermore, the hydroxyl group can be replaced by hydrogen by red phosphorus in the presence of hydriodic acid or iodine whilst heating, for example at ca. 100° to 250°C. In a further preferred procedure, the diphenyl-sulphamoyl group which is optionally substituted in the phenyl moiety is reduced with the assistance of an appropriate, optionally complex hydride, e.g. with an alkali metal borohydride, whilst heating, e.g. at ca. 100° to 200°C.

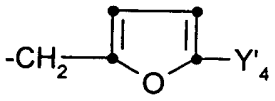
Replacement of the carboxyl group by hydrogen is effected by conventional decarboxylation, i.e. at elevated temperatures, for example in a temperature range of ca. 100° to 300°C, optionally in the presence of a transition metal or an alloy thereof, e.g. copper or copper bronze, or optionally in the presence of a high-boiling amine, e.g. pyridine, quinoline or lutidine.

In a further preferred embodiment of this process variant, the carbonyl group A may be reduced to the methylene group for example analogously to the Clemmensen reduction, e.g. with the assistance of a metallic system comprising a metal component and a hydrogen-yielding component. The metal component used is e.g. optionally amalgamated zinc and the hydrogen-yielding component is e.g. a protonic acid such as hydrochloric acid. The carbonyl group -A- may be similarly reduced to the methylene group analogously to the Wolff-Kishner reaction or the Huang-Minlon variant, e.g. with the assistance of hydrazine in the presence of a base such as an alkali metal hydroxide or an alkali metal lower alkanolate, e.g. sodium hydroxide or potassium tert.-butylate. During this process, under the reaction conditions, hydrazono-methylene -A- may be formed. This is advantageously not isolated and can be converted into the methylene group with a base.

In a further variant of this process, optionally substituted hydrazonomethylene -A- can be reduced to methylene for example with the assistance of an optionally complex hydride, e.g. comprising an alkali metal and an element of the 3rd main group of the Periodic Table, such as sodium borohydride or lithium aluminium hydride.

In compounds of formula (II) which can be converted by oxidation into compounds of formula (I), X_1 is a radical that can be converted by oxidation into the group of formula $-CH_2-COOH$, and X_2 is hydrogen.

A radical X_1 that can be converted by oxidation into the group of formula $-CH_2-COOH$ is for example a group of formula $-CH_2-Y_3$, whereby Y_3 is for example the following groups:

$-CH=CH-Y_4$, $-CH=C(Ar)_2$, $-CHO$, 

wherein Y'_4 is hydrogen or formyl which is optionally acetalised e.g. with a lower alkanol or a lower alkanediol or with a corresponding thio analogue;
$-CH(O)-CH(OH)-Y_4$, $-CH(OH)-CO-Y_4$, $-CH(OH)-COOY_4$, $-CH(NH_2)-CO-Y_4$, $-CO-CO-Y_4$ or $-CO-COOH$, in which Y_4 is hydrogen, an aliphatic radical, e.g. an optionally substituted lower alkyl radical, or an aryl radical. By Ar is understood an aryl radical such as optionally substituted phenyl.

Suitable oxidation agents are for example oxygen in elementary or activated form, whereby suitable transition metals or the oxides thereof, such as manganese, cobalt, iron or vanadium pentoxide, are used for activation, and also ozone, peroxides such as hydrogen peroxide, alkali metal peroxides or peroxides of inorganic mineral acids or organic carboxylic acids, e.g. peroxy-sulphuric acid, peracetic acid, trifluoroperacetic acid, perphthalic acid, perbenzoic acid or m-chloroperbenzoic acid. Also suitable are oxidising compounds of transition metals, especially those of the I, VI, VII or VIII secondary groups of the Periodic Table, such as suitable copper salts, e.g. copper oxides or copper chromite, silver compounds, e.g. silver (I) oxide or silver picolinate, chromium compounds, e.g. chromic acid, chromium trioxide, chromyl chloride or alkali metal chromates or dichromates, ruthenium or osmium compounds, such as the corresponding tetroxides, similarly lead compounds, e.g. lead dioxide or lead (IV) acetate, halo-oxygen compounds such as alkali metal hypochlorites, iodates or periodates, or periodic acid, N-halo-succinimides such as N-bromosuccinimide, furthermore nitrogenous acids or the

anhydrides thereof, such as nitric acid or corresponding nitric oxides, and optionally sulphuric acid. If required, mixtures of the indicated oxidation agents may also be used.

A group of formula $-CH_2-Y_3$ of this kind is preferably oxidised to $-CH_2-COOH$, wherein Y_3 signifies formyl or a group of formula -CO-COOH. The formyl group may be formed *in situ* advantageously in the course of oxidation reactions, or may be released from a derivatised form. The *in situ* formation of formyl is effected in particular from those radicals Y_3 in which Y_3 primarily signifies hydroxymethyl or groups of formulae $-CH=CH-Y_4$, $-CH(OH)-CH(OH)-Y_4$ or $-CH(OH)-CO-Y_4$, also $-CH=C(Ar)_2$, $-CO-CO-Y_4$, $-CH(OH)-COOY_4$ or $-CH(NH_2)-CO-Y_4$.

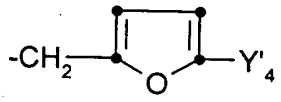
Release of the formyl group Y_3 is effected for example from one of its acetals or imines, as well as from other such formyl-masking groups. Acetalised formyl is e.g. formyl acetalised with lower alkanols or a lower alkanediol, such as di-lower-alkoxymethyl, e.g. dimethoxy- or diethoxymethyl, or such as lower alkylene-dioxymethyl, e.g. ethylene dioxy- or trimethylene dioxymethyl. Imines are e.g. optionally substituted N-benzylimine or N-(2-benzothiazolyl)-imine.

Formyl, hydratised or acetalised formyl Y_3 is *inter alia* oxidised to carboxyl, for example by treatment with a silver compound in the presence of a base, e.g. with silver (I) oxide in sodium hydroxide, with a manganese compound in a basic medium, e.g. with potassium permanganate in a sodium carbonate solution, with a chromium compound in the presence of an acid, e.g. with potassium dichromate in dilute sulphuric acid or with chromium trioxide in glacial acetic acid.

Oxidation of the group of formula -CO-COOH is effected e.g. by treatment with a peroxide, e.g. in the presence of a base such as hydrogen peroxide in a sodium hydroxide solution, or with concentrated sulphuric acid.

Oxidation of the remaining radicals Y_3 to carboxyl may advantageously be effected *in situ*, optionally via the formyl step, and is otherwise carried out as follows: Y_3 $-CH(OH)-COOY_4$, $-CH=CH-Y_4$ and $-CH(OH)-C(OH)-Y_4$ with the assistance of a halo-oxygen compound such as a periodate compound, e.g. with the assistance of sodium periodate, advantageously in the presence of catalytic quantities of a manganese compound such as potassium permanganate, Y_3 hydroxymethyl, $-CH(NH_2)-CO-Y_4$, $-CH(OH)-CO-Y_4$ and $-CO-CO-Y_4$ with the assistance of a manganese compound, optionally in the presence of a base, e.g. by treatment with potassium permanganate in a sodium carbonate solution, with the assistance of a chromium compound, optionally in the presence of an acid, e.g. by treatment with potassium dichromate in dilute

hydrochloric acid solution or with chromium trioxide in glacial acetic acid, or by concentrated nitric acid, also by treatment with a peroxide, e.g. with hydrogen peroxide, optionally in the presence of a base, e.g. sodium hydroxide solution. Oxidation of Y_3 -CH=C$(Ar)_2$, Ar signifying in particular phenyl, is effected e.g. analogously to the Barbier-Wieland reaction, with chromium trioxide in an acid, e.g. glacial acetic acid.

If X_1 of formula (II) signifies e.g. a group of formula 

this may be converted by oxidation to the group of formula -CH_2-COOH e.g. advantageously with ozone and hydrogen peroxide in an inert solvent, e.g. in a ketone such as acetone.

When using the said oxidation agents, depending on the choice of oxidation agent, the process is frequently effected in the presence of bases such as alkali metal or alkaline earth metal hydroxides or carbonates, e.g. sodium, potassium or calcium hydroxide or sodium, potassium or calcium carbonate, or amines, e.g. cyclic amines, for example pyridine or quinoline, or e.g. lower alkylamines, for example triethylamine or diisopropylamine, or in the presence of protonic acids such as mineral acids, e.g. sulphuric acid, a phosphoric or hydrohalic acid, organic carboxylic acids, e.g. lower alkanecarboxylic acid, or sulphonic acids, e.g. lower alkanecarboxylic acids or optionally substituted benzenesulphonic acids. Oxidation is effected in known manner in an inert solvent or diluent, and if necessary with cooling or heating, e.g. in a temperature range of ca. -30° to boiling point of the relevant solvent.

Variant b):

Halogen X_3 or X_4 primarily signifies bromine or iodine, also chlorine.

The reaction of compounds of formula IIIa with those of formula IIIb takes place in the presence of a catalytic agent and at elevated temperature, e.g. in a temperature range of ca. 50° to 300°C, especially between ca. 100° and 200°C, whereby an appropriate high-boiling inert solvent is used, such as an aromatic hydrocarbon, e.g. toluene or an xylene, a lower alkanol, e.g. amyl alcohol, a sulphoxide, e.g. dimethyl sulphoxide, an amide, e.g. dimethyl formamide, hexamethylphosphoric acid triamide or N-methylpyrrolidone.

The catalytic agent may be for example elementary copper, primarily copper existing in activated form and/or copper salts, such as corresponding halides such as chlorides, bromides

or iodides, sulphates or oxides; preferred salts are copper (I) salts. Furthermore, an alkali metal or alkaline earth metal halide, such as sodium or potassium iodide, may advantageously be added. Normally, at least one equivalent of an appropriate base is added to the reaction mixture, especially an alkali metal carbonate, e.g. potassium carbonate. An amine such as pyridine is also suitable.

The starting materials of formulae (II), (IIIa) and (IIIb) employed are partly known or may be produced in known manner.

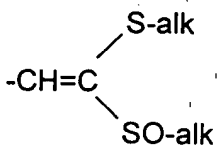
To produce starting materials of formula (II), wherein X_1 signifies a radical that can be converted hydrolytically into the group of formula $-CH_2-COOH$ and X_2 is hydrogen, the process starts for example with 2-(Ph-NH)-benzoic acid and the carboxyl group is reduced to the corresponding hydroxymethyl group, with a complex hydride such as lithium aluminium hydride being used for example as the reduction agent. After exchanging the hydroxyl group for a halogen atom, e.g. by treatment with a halogenation reagent such as phosphorus tribromide, and replacing the halogen atom with the cyano group, e.g. by a reaction with sodium cyanide, the [2-(Ph-amino)-phenyl]-acetonitrile is obtained. From this, in turn, e.g. by treatment with an alkanol in the presence of a strong acid, the corresponding alkoxycarbamidoyl compounds are obtainable, then by treatment with hydrogen peroxide in the presence of a protonic acid the corresponding carbamoyl compound is obtainable, by treatment with hydrogen sulphide in the presence of an inorganic base the corresponding thiocarbanoyl derivative is obtained, and by a reaction with an excess of alcohol and in the presence of a mineral acid corresponding esters are obtainable. From the alkoxycarbamidoyl compounds, in turn, by treatment with ammonia, or a primary or secondary amine, the corresponding amidino compounds are produced and/or by a reaction with at least 2 equivalents of an alkanol, the corresponding trialkoxymethyl derivatives are produced.

Starting with esters, the corresponding acid chloride is obtained for example by a reaction with phosgene, and from the acid chloride in turn, e.g. by treatment with a carboxylic acid, a corresponding anhydride may be produced, or by a reaction with hydrogen sulphide and/or phosphorus pentasulphide, the thio- or dithiocarboxyl derivative may be produced.

A further method of producing compounds of formula (II), wherein X_1 signifies a radical that can be converted hydrolytically or acidolytically into the group of formula $-CH_2-COOH$ and X_2 is hydrogen, consists in reacting derivatives such as esters or amides, especially also N,N-di-

lower-alkylamides, or 2-halogen- such as 2-bromo- or 2-iodo-phenylacetic acid, with Ph-NH_2 in the presence of activated copper at an elevated temperature, e.g. at ca. 120° to 200°C, and adding at least 1 mol of potassium carbonate. In this way, corresponding esters or amides, 2-oxazolidinyl derivatives or the nitrile of formula (II) are obtainable in particular.

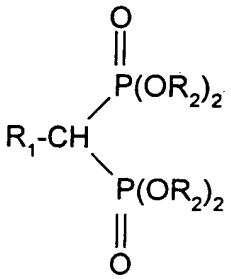
To produce compounds of formula (II), wherein X_1 is a group of formula



the process starts for example with the 2-(Ph-NH)-benzaldehyde, and this is reacted for example with a formaldehyde-dialkyl-mercaptal-S-oxide, e.g. with formaldehyde-dimethyl-mercaptal-S-oxide, in the presence of a base such as an alkali metal hydroxide, e.g. sodium hydroxide.

Compounds of formula (II), wherein X_1 and X_2 together represent an oxo-ethylene group which is linked via the carbonyl-carbon atom to the aniline-nitrogen atom, may be obtained for example by acylating e.g. a compound of formula Ph-NH-C_6H_5 with 2-chloroacetyl chloride, and cyclising the 2-chloroacetamide thus obtainable in the presence of a Lewis acid to the corresponding indolin-2-one derivative.

Compounds of formula (II), wherein X_1 and X_2 together represent a group of formula -CH=C(R_1)-P(=O)-(OR_2)- which is linked by the phosphorus atom to the anilino-nitrogen atom may be produced for example from the 2-(Ph-NH)-benzaldehyde, reacting it e.g. with a N-substituted aminomethylene-tetraalkyl-diphosphonate of formula



(IIa),

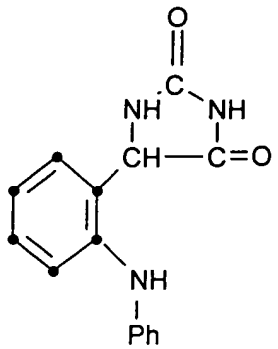
wherein R_1 is a disubstituted amino group and R_2 is alkyl, whereby the process may be advantageously carried out in the presence of equimolar quantities of a base such as an alkali metal hydride, e.g. sodium hydride, and optionally whilst heating.

To produce compounds of formula (II), wherein X_1 is a group of formula -CH(Y_2)-COOH, in which Y_2 signifies hydroxyl and X_2 signifies hydrogen, the process starts e.g. with

2-(Ph-NH)-benzoic acid, this is converted by halogenation, e.g. with thionyl chloride, to the corresponding acid halide, and the halogen atom is exchanged for the cyano group by reacting with copper (I) cyanide. After hydrolysis of the cyano group, e.g. with 37% hydrochloric acid, and subsequent alkaline cleavage of the resulting indolin-2,3-dione, the oxo group in the 2-[2-(Ph-NH)-phenyl]-2-oxo-acetic acid which is obtainable in this way is reduced to the hydroxyl group X_1, whereby a complex hydride such as sodium borohydride or red phosphorus and iodine may be used e.g. as the reduction agent.

To produce compounds of formula (II), wherein X_1 is a group of formula -CH(Y_2)-COOH, in which Y_2 is lower alkylthio, especially methylthio, and X_2 signifies hydrogen, the process starts e.g. with Ph-NH-C_6H_5, which is N-acylated with a lower alkylthio acetyl chloride. Following halogenation, e.g. with N-chlorosuccinimide, the resulting N-(phenyl)-N-Ph-2-halogen-2-lower-alkylthio-acetamide may be cyclised in the presence of a Lewis acid, e.g. tin chloride, to a 3-lower-alkylthio-indolin-2-one. From this, e.g. by means of alkaline hydrolysis, optionally via an ester to be formed, a compound of formula (II) may be obtained, in which X_1 is a group of formula -CH(Y_2)-COOH, wherein Y_2 signifies lower alkylthio, especially methylthio, and X_2 is hydrogen.

To produce compounds of formula (II), wherein X_1 is a group of formula -CH(Y_2)-COOH, in which Y_2 signifies a dialkylamino group, especially a dimethylamino group or a diphenyl-sulphamoyl group which is optionally substituted in the phenyl moiety, and X_2 is hydrogen, the process starts e.g. with 2-(Ph-amino)-benzaldehyde, which is reacted with sodium cyanide and ammonium carbonate to the hydantoin of formula



(IIb) .

Following alkaline hydrolysis of the compound of formula (IIb) to the correspondingly substituted 2-amino-2-phenyl-acetic acid, the amino group may be alkylated by known methods, e.g. with a lower alkyl halide in the presence of a base, or acylated e.g. with a phenyl-sulphonyl halide which is optionally substituted in the phenyl moiety. If necessary, the amino group of the anilino

radical can be protected during the reaction sequence and the protecting group cleaved again prior to removal of the group Y_2.

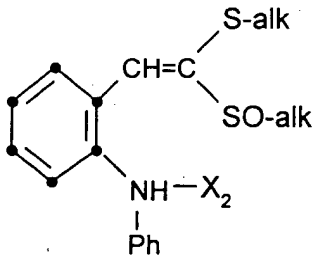
To produce compounds of formula (II), wherein X_1 is a group of formula -A-COOH, in which -A- is optionally substituted hydrazonomethylene and X_2 is hydrogen, the process starts for example with 2-[2-(Ph-NH)-phenyl]-2-oxoacetic acid, which is treated with a corresponding hydrazine. This reaction may advantageously take place in the presence of a base, such as an alkali metal hydroxide, e.g. sodium hydroxide, or an alkali metal alkanolate, e.g. potassium tert.-butylate.

To produce compounds of formula (II), wherein X_1 is a radical that can be converted by oxidation into the group of formula $-CH_2-COOH$ and X_2 is hydrogen, the process starts for example with 2-(Ph-NH)-benzoic acid, and the carboxyl group is reduced to the hydroxymethyl group, whereby a complex hydride such as lithium aluminium hydride is used e.g. as the reduction agent. After substitution of the hydroxyl group with a halogen atom, e.g. by treatment with a halogenation reagent such as thionyl chloride, the resulting methyl halide compound is reacted e.g. with a halide of formula Hal-Y_3 in the presence of magnesium and copper (I) iodide. Preferred compounds of formula Hal-Y_3 are for example those in which Y_3 denotes the groups of formula $-CH=CH-Y_4$ or $-CH=C(Ar)_2$. From the compounds of formula II thus obtainable, in which X_1 is a group of formula $-CH_2-Y_3$ and Y_3 is $-CH=CH-Y_4$ and X_2 is hydrogen, by ozonolysis and cleavage of the ozonide by zinc/glacial acetic acid, compounds of formula (II) may be obtained in which X_1 is the group of formula $-CH_2Y_3$, Y_3 is formyl and X_2 signifies hydrogen, or by hydroxylation of the double bond, e.g. with osmium tetroxide, with partial or total oxidation of the hydroxyl compounds thus obtained, corresponding oxo derivatives may be obtained or compounds in which Y_3 denotes the following groups: $-CH(OH)-CH(OH)-Y_4$, $-CH(OH)-CO-Y_4$ or $-CO-CO-Y_4$.

The corresponding α-keto-carboxylic acid of formula (II), wherein X_1 is a group of formula $-CH_2-Y_3$, Y_3 is the group of formula -CO-COOH and X_2 is hydrogen, is obtainable e.g. by treating an ester of [2-(Ph-amino)-phenyl]-acetic acid with phosgene and reacting the resulting acid chloride e.g. with sodium cyanide, and hydrolysing the cyano group to the carboxyl group.

By esterification of the 3-[2-(Ph-NH)-phenyl]-2-oxo-propionic acid obtainable in this way, compounds of formula (II) may also be produced, wherein X_1 signifies a group of formula $-CH_2-Y_3$ and X_2 signifies hydrogen, Y_3 is the group $-CO-CO-OY_4$ and Y_4 signifies hydrogen, an aliphatic radical or an aryl radical.

One method of producing the starting material of formula (II), wherein X_1 is the group of formula $-CH_2-COOH$ and X_2 is an appropriate amino protecting group that can be converted into hydrogen, consists for example in starting with 2-(Ph-NH)-benzaldehyde and introducing the desired amino protecting group X_2 in conventional manner. In the next reaction steps, the acetic acid side chain may be built up from the formyl group. This may take place e.g. by reacting the relevant benzaldehyde with formaldehyde-dialkyl-mercaptal-S-oxide, such as formaldehyde-dimethylmercaptal-S-oxide, e.g. in the presence of a base such as an alkali metal hydride, for example sodium hydride. The resulting compound of formula



(IIb),

wherein alk is alkyl, especially lower alkyl, may subsequently be treated with an acid and a lower alkanol, e.g. with hydrochloric acid and methanol, and thus converted into the corresponding ester of formula (II). After alkaline hydrolysis, e.g. with a sodium hydroxide solution and if necessary whilst heating, the corresponding compound of formula (II) may be obtained e.g. in the form of its alkali metal salt.

Introduction of an acyl radical X_2 is effected for example by reacting the amino group with a corresponding anhydride, especially in the presence of a base. The anhydrides in question may be for example symmetric or asymmetric anhydrides, e.g. with an optionally substituted lower alkanecarboxylic acid such as acetic acid or trifluoroacetic acid, or with a mineral acid such as hydrohalic acid.

Since, in some cases, such anhydrides are unstable, activated esters may be used instead, such as 4-nitrophenyl ester.

Individually, acetyl or trifluoroacetyl is introduced for example by a reaction with the symmetric anhydride or a corresponding halide, such as chloride, while the tert.-butyloxycarbonyl group may be formed e.g. from the tert.-butyl-(4-nitrophenyl)-carbonate and the benzyloxycarbonyl or p-toluenesulphonyl group from the respective halide, such as the chloride.

Phenylthio or 1-phenyl-lower-alkyl radicals which are optionally substituted by nitro may be introduced e.g. from the respective halide, such as bromide or chloride.

The bases may be for example inorganic or organic bases, whereby suitable inorganic bases are e.g. hydroxides, carbonates or oxides of elements of the 1st and 2nd main groups of the Periodic Table, especially sodium hydroxide, sodium carbonate or magnesium oxide. Organic amines are e.g. lower alkylamines such as triethylamine, or cyclic amines such as pyridine.

Formyl may be introduced e.g. by reacting the amine with formic acid in acetic anhydride.

Introduction of a 2-lower-alkenyl group, especially allyl, may be effected for example by a reaction with a 2-lower-alkenyl bromide, e.g. allyl bromide, the process advantageously taking place in the presence of a base, such as an alkali metal hydride, e.g. sodium hydride. In analogous manner, a benzyl group may be similarly introduced for example, by treatment with a corresponding halide such as benzyl bromide.

The compounds of formulae (IIIa) and (IIIb) are known or may be produced in analogous manner.

As a result of the close relationship between the new compound in free form and in the form of its salts, in the preceding and following description, the free compound or its salts are understood to be *mutatis mutandis* also the corresponding salts or the free compound.

The free compound of formula (I) obtained may be converted in known manner into salts, the acid being treated with the desired base.

The salts obtained may be converted in known manner into the free compound, e.g. by treatment with an acidic reagent such as a mineral acid.

The invention also relates to those embodiments of the process by which the procedure starts with a compound obtainable as an intermediate at any stage of the process and the missing steps are then carried out, or a starting material is used optionally in the form of a salt or is formed in particular under the reaction conditions.

In the process of the present invention, preferably the starting materials used are those which lead to the compounds portrayed at the beginning as especially valuable. New starting materials, their use, e.g. as active ingredients for medicaments, formulation processes and processes for their production similarly form objects of the invention.

The pharmaceutical preparations according to the invention, which contain the compound according to the invention or pharmaceutically acceptable salts thereof, are those used for topical application, also for enteral, such as oral or rectal, and parenteral administration to warm-blooded animal(s), whereby the pharmacological active ingredient contained therein is on its own or together with a pharmaceutically acceptable substrate. The daily dosage of the active ingredient depends on the age and individual condition, as well as on the type of application.

The new pharmaceutical preparations contain e.g. from ca. 10% to 80%, preferably from ca. 20% to 60% of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are e.g. those in single dose forms, such as dragées, tablets, capsules or suppositories, and also ampoules. These are produced in known manner, e.g. by conventional mixing, granulating, dragée-forming, dissolving or lyophilising processes. In this way, pharmaceutical preparations for oral application may be obtained by combining the active ingredient with solid substrates, optionally granulating the mixture obtained, and processing the mixture or granulate into tablets or dragée cores, if desired or if necessary, after adding suitable excipients.

Suitable substrates are in particular fillers such as sugar, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate, also binders such as starch paste, using e.g. cornstarch, wheat starch, rice starch or potato starch, gelatins, tragacanth, methyl cellulose and/or polyvinyl pyrrolidone, if desired, disintegrants, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are primarily flow agents, regulating agents and lubricants, e.g. silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which are optionally resistant to gastric juices, using *inter alia* concentrated sugar solutions which optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in appropriate organic solvents or solvent mixtures, or in order to produce coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetyl

cellulose phthalate or hydroxypropylmethyl cellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings e.g. to identify or characterise different doses of active ingredient.

Further orally employable pharmaceutical preparations are hard gelatin capsules, as well as soft, closed capsules consisting of gelatin and a softener such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of a granulate, e.g. mixed with fillers such as lactose, binding agents such as starches, and/or lubricants such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in appropriate liquids such as fatty oils, paraffin oil or liquid polyethylene glycol, whereby stabilisers may similarly be added.

The rectally administrable pharmaceutical preparations in question are for example suppositories, which consist of a combination of the active ingredient with a suppository matrix. Suitable suppository matrices are for example natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. In addition, rectal gelatin capsules may also be used, and these contain a combination of the active ingredient with a base material. The base materials in question may be e.g. liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, e.g. a water-soluble salt, are primarily suitable, also suspensions of the active ingredient such as corresponding oily injection suspensions, using appropriate lipophilic solvents or vehicles such as fatty oils, e.g. sesame oil, or synthetic fatty acid esters, e.g. ethyloleate or triglycerides, or aqueous injection suspensions containing viscosity-increasing substances, e.g. sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally also containing stabilisers.

Pharmaceutical preparations for topical application may be primarily creams, ointments, pastes, foams, tinctures and solutions, which contain from ca. 0.1 to 5 % of active ingredient.

Creams are oil-in-water emulsions which have more than 50 % water. The oily base employed may be primarily fat alcohols, e.g. lauryl, cetyl or stearyl alcohol, fatty acids, e.g. palmitic or stearic acid, liquid to solid waxes, e.g. isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, e.g. petroleum jelly (Petrolatum) or paraffin oil. The emulsifiers in question are surface-active substances having predominantly hydrophilic properties, such as corresponding

non-ionic emulsifiers, e.g. fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid ester or polyoxyethylene sorbitan fatty acid esters (Tweens), and also polyoxyethylene fatty alcohol ethers or fatty acid esters, or corresponding ionic emulsifiers, such as alkali metal salts of fat alcohol sulphates, e.g. sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are normally used in the presence of fat alcohols, e.g. cetyl alcohol or stearyl alcohol. Additives to the water phase are *inter alia* agents which prevent the creams from drying out, e.g. polyalcohol such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives, odoriferous substances, etc.

Ointments are water-in-oil emulsions which contain up to 70 %, preferably however from ca. 20 % to 50 % water or contain aqueous phases. The fat phase may be primarily hydrocarbons, e.g. petroleum jelly, paraffin oil and/or hard paraffins, which contain preferably appropriate hydroxyl compounds such as fat alcohols or esters thereof, e.g. cetyl alcohol or wool wax alcohols or wool waxes, to improve the water-binding capability. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid ester (Spans), e.g. sorbitan oleate and/or sorbitan isostearate. Additives to the water phase are *inter alia* moisture-retaining agents such as polyalcohols, e.g. glycerol, propylene glycol, sorbitol and/or polyethylene glycol, as well as preservatives, odoriferous substances, etc.

Fat ointments are water-free and contain as the base, in particular, a hydrocarbon, for example paraffin, petroleum jelly and/or liquid paraffins, furthermore natural or semi-synthetic fat, e.g. coconut oil triglyceride, or preferably hardened oils, for example hydrated peanut oil or castor oil, furthermore fatty acid partial esters of glycerol, for example glycerol mono- and distearate, as well as e.g. the fat alcohols, emulsifiers and/or additives mentioned in connection with the ointments, which increase the ability to absorb water.

Pastes are creams and ointments with secretion-absorbing powder constituents, such as metal oxides, e.g. titanium oxide or zinc oxide, also talc and/or aluminium silicates, which have the task of binding moisture or secretion which may be present.

Foams are administered e.g. from pressurised containers and are for example liquid oil-in-water emulsions present in aerosol form, whereby halogenated hydrocarbons such as chlorofluoro lower alkanes, e.g. dichloride fluoromethane and dichlorotetrafluoroethane, are used as propellants. The oil phase employed is *inter alia* hydrocarbons, e.g. paraffin oil, fat alcohols, e.g. cetyl alcohol, fatty acid esters, e.g. isopropyl myristate, and/or other waxes. The emulsifiers

employed are *inter alia* mixtures of those with predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens), and those with predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). They also include the usual additives, such as preservatives, etc.

Tinctures and solutions usually have an aqueous-ethanolic base, to which are added *inter alia* polyalcohols, e.g. glycerol, glycols and/or polyethylene glycol, moisture retaining agents to reduce evaporation and refatting substances such as fatty acid esters with low polyethylene glycols, i.e. lipophilic substances that are soluble in the aqueous mixture, as a replacement for the fat substances removed from the skin by the ethanol, and, if necessary, other excipients and additives.

Preparation of the topically applicable pharmaceutical preparations takes place in known manner, e.g. by dissolving or suspending the active ingredient in the base or in a part thereof, if necessary. When processing the active ingredient as a solution, it is normally dissolved in one of the two phases before emulsification; when processing it as a suspension, it is mixed with part of the base after emulsification and then added to the remainder of the formulation.

Dosaging of the active ingredient depends on the warm-blooded species, the age and the individual condition, as well as the method of application. Under normal circumstances, for oral application to a warm-blooded person of ca. 75 kg, an approximate daily dose of ca. 50 to 600 mg , advantageously in several equal part doses, is estimated.

The following examples illustrate the above-described invention; however, they should in no way restrict the scope of the invention. Temperatures are given in degrees Celsius.

Example 1:

A solution of 10.5 g of 1-(2-chloro-6-fluorophenyl)-2-indolinone in 18 ml of ethanol, 25 ml of water and 13 g of a 20% sodium hydroxide solution is heated under reflux for 4 hours. The warm solution is treated with activated carbon and subsequently filtered. The crystals which precipitate upon cooling to 0° are filtered off and recrystallised from water. The sodium-2-(2-chloro-6-fluoroanilino)-phenyl-acetate is thus obtained with a m.p. of 270° (decomp.).

The starting material may be produced for example as follows:

107 g of 2-chloro-6-fluoro-benzoic acid are added whilst stirring to 146 g of thionyl chloride. The mixture is subsequently heated under reflux, and excess thionyl chloride is then distilled off at normal pressure. The fraction which boils at 95° at 14 torr contains 2-chloro-6-fluoro-benzoyl chloride.

75 g of 2-chloro-6-fluoro-benzoyl chloride are added dropwise whilst stirring, at room temperature, to 300 g of an approximately 15% aqueous ammonia solution. After stirring for one hour at 0°, the precipitated product is filtered off, washed with water and dried in a vacuum drying chamber at 40°. 2-chloro-6-fluoro-benzamide with a m.p. of 142° is thus obtained.

125 g of a 13% sodium hypochlorite solution are added dropwise at 0° to 5° to a suspension of 30 g of 2-chloro-6-fluoro-benzamide in 250 ml of 2 N sodium hydroxide solution. The reaction mixture is subsequently heated in stages to 100°. Then steam is passed in, and the 2-chloro-6-fluoroaniline formed is distilled with steam. The distillate is extracted twice with 200 ml of toluene, dried over sodium sulphate and filtered. 10.8 g of acetyl chloride are added dropwise at 20° to the combined toluene extracts. The reaction mixture is slowly heated to reflux temperature and maintained at reflux for 1 hour. The 2-chloro-6-fluoroacetamide which precipitates during the subsequent cooling to 0° is filtered, washed with toluene and dried in a vacuum drying chamber at 50°. M.p. 135°.

25 g of 2-chloro-6-fluoroacetamide, 1 g of copper (I) oxide and 11.5 g of potassium carbonate are heated together to 140° in 400 ml of bromobenzene. After boiling at reflux for 16 hours, the mixture is cooled to room temperature and filtered. After adding isopropanol, the N-(2-chloro-6-fluorophenyl)-N-phenylacetamide crystallises. M.p. 95° - 96°.

30 g of N-(2-chloro-6-fluorophenyl)-N-phenyl-acetamide are boiled for 5 hours in 180 ml of 10% ethanolic potassium hydroxide solution. The solution is subsequently evaporated to dryness, the residue mixed with 100 ml of water and extracted with 150 ml of toluene. The residue is dried over sodium sulphate, and the filtered toluene extracts are evaporated to dryness at 15 torr. The residue is distilled under a high vacuum. The N-(2-chloro-6-fluorophenyl)-N-phenyl-amine obtained boils at 78°/0.05 torr and melts at 71° - 72°.

10 g of chloracetyl chloride are added dropwise to 17.7 g of N-(2-chloro-6-fluoro-phenyl)-N-phenylamine at 120° - 130°. When the hydrogen chloride has finished forming, 30 ml of ethyl cellulose are added. Upon cooling, the N-(2-chloro-6-fluorophenyl)-N-phenyl-2-chloroacetamide crystallises. M.p. 91° - 92°.

18.5 g of N-(2-chloro-6-fluorophenyl)-N-phenyl-2-chloroacetamide and 19.5 g of aluminium chloride are thoroughly mixed and heated for 2 hours to 150° - 170°. The melt is cooled, added to ice water and extracted with 150 ml of methylene chloride. The extract is washed with water until neutral and subsequently evaporated to dryness. The residue is dissolved in 40 ml of ethanol at 75°, treated with activated carbon and filtered. Upon cooling, the 1-(2-chloro-6-fluoro-phenyl)-2-indolinone crystallises. M.p. 85° - 87°.

Example 2:

A mixture of 7.1 g of o-iodo-phenylacetic acid potassium salt, 19.2 g of 2-chloro-6-fluoro-aniline, 11.5 g of potassium carbonate, 0.8 g of copper powder [activated in accordance with Org. Synth. Coll., Vol. III, 339 (1955)] and 50 ml of n-amyl-alcohol is heated whilst stirring for 9 hours at 120°C with nitrogen gas being passed in. During the reaction, n-amyl-alcohol is slowly distilled off through a descending condenser, whereby the distilled solvent is continuously replaced by adding fresh n-amyl-alcohol. The reaction mixture is cooled and evaporated to dryness at 60° under reduced pressure. 30 ml of water and 30 ml of ether are added to the residue. The mixture is filtered through 5 g of Hyflo. The Hyflo is washed with 10 ml of water. In the filtrate, the aqueous phase is separated and extracted twice, each time with 50 ml of ether. The combined ether extracts are washed twice, each time with 25 ml of water, dried over magnesium sulphate and concentrated to dryness under reduced pressure. The crystalline residue, [2-[(2-chloro-6-fluoro-phenyl)-amino]-phenyl]-acetic acid, is dissolved whilst heating in 20 ml of a 20% sodium carbonate solution. When the solution cools, the sodium salt of [2-[(2-chloro-6-fluoro-phenyl)-amino]-phenyl]-acetic acid crystallises. M.p. 265° with decomposition.

Example 3:

Tablets containing 25 mg of active ingredient, e.g. sodium-2-(2-chloro-6-fluoro-anilino)-phenyl-acetate, may be produced as follows:

Constituents (for 1000 tablets):

active ingredient	25.0 g
lactose	100.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

Preparation:

All solid ingredients are first of all forced through a sieve of 0.6 mm mesh size. Then, the active ingredient, the lactose, the talc, the magnesium stearate and half of the starch are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The starch paste obtained is added to the principal amount, and the mixture is granulated, if necessary adding water. The granulate is dried over night at 35°, forced through a sieve of 1.2 mm mesh size, and pressed into tablets of ca. 6 mm diameter which are concave on both sides.

Example 4:

Chewable tablets containing 30 mg active ingredient, e.g. sodium-2-(2-chloro-6-fluoro-anilino)-phenyl-acetate, may be prepared e.g. as follows:

Composition (for 1000 tablets):

active ingredient	30.0 g
mannitol	267.0 g
lactose	179.5 g
talc	20.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharine	1.0 g
5% gelatin solution	q.s.

Preparation:

All solid ingredients are first of all forced through a sieve of 0.25 mm mesh size. The mannitol and the lactose are mixed, granulated whilst adding gelatin solution, forced through a sieve of 2 mm mesh size, dried at 50° and again forced through a sieve of 1.7 mm mesh size. The active ingredient, the glycine and the saccharine are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc added, the whole preparation is thoroughly mixed and pressed into tablets of ca. 100 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 5:

Tablets containing 100 mg of active ingredient, e.g. sodium-2-(2-chloro-6-fluoro-anilino)-phenyl-acetate, may be prepared e.g. as follows:

Composition (for 1000 tablets):

active ingredient	100.0 g
lactose	248.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	15.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Preparation:

The solid ingredients are first of all forced through a sieve of 0.6 mm mesh size. Then, the active ingredient, the lactose, the talc, the magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The paste obtained is added to the powdery substances, and the whole mixture is mixed and granulated, if necessary adding water. The granulate is dried over night at 35°, forced through a sieve of 1.2 mm mesh size, and pressed into tablets of ca. 10 mm diameter which are concave on both sides and scored on the upper side.